

Application No. 09/498,046
Response Dated April 13, 2005 to
January 13, 2005 Office Action

REMARKS

Claims 26-32, 34, 36-41, 46, and 52-57 are currently under consideration.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 34 stands rejected for indefiniteness because the limitation “antigen” has no antecedent basis. The claim has been amended to correct this error. The rejection can now be withdrawn.

Rejection Under 35 U.S.C. § 112, first paragraph

All of the pending claims stand rejected for lack of enablement. The question remains to be whether Heinen¹ shows that the claimed vaccines exacerbate flu symptoms in pigs, and therefore casts doubt on the efficacy of the claimed vaccines. In addition, the Examiner has cited two new documents – Jegerlehner² and Chen³ – to support the rejection.

Jegerlehner

The Examiner rebuts applicants’ arguments by citing Jegerlehner, which is said to provide “contradictory evidence” to applicants’ data and Fan’s teachings. Specifically, the Examiner quotes Jegerlehner as saying that the M2e-HBc vaccine would be “insufficient during the yearly epidemics . . . and is clearly inferior to protection achieved by immunization with classical inactivated viral preparations” (the Abstract). Applicants respectfully traverse.

¹ Heinen et al., Journal of General Virology 83:1851-9 (2002).

² Jegerlehner et al., Journal of Immunology 172:5598-5605 (2004).

³ Chen et al., Vaccine 19:1446-55 (2001).

Application No. 09/498,046
Response Dated April 13, 2005 to
January 13, 2005 Office Action

While Jegerlehner states that the M2e-HBc vaccine may be inferior to classical inactivated viral preparations for yearly epidemics, that document touts the merit of using the M2e-HBc vaccine during a *pandemic*:

... [I]mmunization with the M2-HBc vaccine may be considered as a precaution to prevent or at least reduce mortality during a *pandemic*. . . . [I]t can be assumed that the M2-HBc vaccine would [] have been effective against the 1918 pandemic. Reemergence of a 1918 or 1918-like influenza virus, whether through natural means or as result of bioterrorism is of *significant* concern, as the 1918 pandemic killed 20-40 million people worldwide. From this point of view, the M2-HBc vaccine may represent a *well-chosen influenza prophylaxis*, especially considering the dangers of producing a 1918-like influenza virus for the purposes of vaccine production. (p. 5605, left col.)

Thus, Jegerlehner validates the usefulness of the claimed vaccines in protecting against an influenza infection.¹

A number of publications by other groups also support the protectiveness of the claimed vaccines. For instance, Mozdzanowska² discusses that influenza A vaccines of the instant invention are protective:

The protective efficacy of actively induced M2-specific immunity was investigated by several groups of investigators who tested various types of vaccine constructs and vaccination modalities. . . . All of these later vaccination protocols induced *significant protection*, both in terms of reduction in virus growth and mortality.

... We found that intranasal (i.n.) administration of M2e-MAPs together with cholera toxin (CT) and a synthetic oligodeoxynucleotide (ODN) with a

¹ The danger of a pandemic is also underscored by the recent scare concerning the distribution of the 1957 pandemic influenza strain to nearly 5,000 laboratories. See *The New York Times*, April 13, 2005 (Exhibit 1). The 1957 pandemic strain killed 1 to 4 million people. *Id.* That strain “has not been included in the flu vaccine since 1968, and anyone born after that date has no immunity to it.” *Id.*

² Mozdzanowska et al., Vaccine 21:2616-26 (2003) (Exhibit 2).

Application No. 09/498,046
Response Dated April 13, 2005 to
January 13, 2005 Office Action

stimulatory CpG motive induced strong M2e-specific antibody titers in serum of mice and resulted in ***significant protection*** against influenza virus challenge. (p. 2617, left col.)

. . . [T]aken together, these studies have now ***clearly*** established that actively induced M2-specific immunity can provide ***significant resistance*** against influenza virus replication in the respiratory tract of mice. . . . In view of the ***strong*** mouse data, it appears worthwhile to investigate more thoroughly M2e-specific immunity in humans. (p. 2625, left col.)

In sum, a large body of data, by applicants and other groups (including Jegerlehner), have demonstrated that the claimed vaccines are protective against and/or during an influenza infection.

Chen

The Examiner cites Chen for disclosing that the NB protein from human influenza B fails to provide protection against influenza virus B infection, and thus in combination with Heinen and Jegerlehner, would cast doubt on the protectiveness of the claimed influenza B and C vaccines. Specifically, the Examiner states that Chen “clearly show that NB, derived from human influenza virus B, fails to provide protection against influenza virus B, see the abstract and Table 2.” Office Action, p. 9.

Applicants traverse. Chen used a plasmid encoding the NB protein for vaccination. The NB protein, like the M2 protein, has a very small external domain. Proteins with such a small external domain are known to be not or nearly not immunogenic in their natural context. However, applicants discovered that these small external domains could become highly immunogenic when linked them to a carrier, and that the elicited antibodies were protective *in vivo*. In fact, the homology between the external domain of the M2 protein and that of the NB

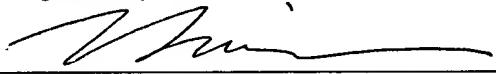
Application No. 09/498,046
Response Dated April 13, 2005 to
January 13, 2005 Office Action

protein results in cross-protection against influenza B virus replication by anti-M2e antibodies, as reported by Liu (see, e.g. the Abstract).¹ In sum, Chen does not address the protectiveness of antibodies elicited by the NB external domain linked to a carrier, as required by the claims.

CONCLUSION

Applicants respectfully submit that the application is in condition for allowance. To expedite prosecution, the Examiner is invited to telephone the undersigned to discuss any issues remaining in this application.

Respectfully submitted,



James F. Haley, Jr. (Reg. No. 27,794)
Z. Ying Li (Reg. No. 42,800)
Attorneys for Applicants

c/o FISH & NEAVE IP GROUP
ROPES & GRAY LLP
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1104
Tel.: (212) 596-9000
Fax.: (212) 596-9090

¹ Liu et al., FEMS Immunology and Medical Microbiology 35:141-46 (2003) (Exhibit 3).